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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/563,464	02/14/2006	Kristofer Olofsson	059490-5048-US	1368

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EXAMINER	
BARKER, MICHAEL P	

ART UNIT	PAPER NUMBER
1626	

MAIL DATE	DELIVERY MODE
06/27/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/563,464	OLOFSSON ET AL.	
	Examiner	Art Unit	
	MICHAEL P. BARKER	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04/17/2008, Response to Restriction*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,14,32-35,37 38,40,and 41* is/are rejected.

7)☒ Claim(s) *1,3-13,15-31,36 and 39* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :01/05/06;04/18/06;06/14/07;01/11/08.

DETAILED ACTION

Claims 1-42 are pending in this Application.

Rejected Claims: 2, 14, 32-35, 37, and 38.

Information Disclosure Statement

The information disclosure statements filed 04/18/2006 and 01/11/2008 fail to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

The information disclosure statements (IDS) submitted on 01/05/2006 and 06/14/2007 were correctly filed. The submissions are in compliance with the provisions of 37 CFR 1.97. Accordingly, the IDS's were considered by the Examiner. Please refer to Applicant's copies of PTO-1449, submitted herewith.

Response to Restriction Requirement

Applicant's election *without traverse* of Group II, i.e. compound of formula I, in which X is an optionally substituted amide, amine, or sulfonamide group, including their compositions and methods of use, as well as the species depicted in Example 131 of the Specification, in the reply filed on November 7, 2006 is acknowledged. The compounds and compositions of Group II are free of prior art. The rejections which follow relate to formalities and enablement of the method claims, 32-35. The subject matter of Group I, wherein X is an optionally

substituted aryl or heteroaryl group, is withdrawn from further consideration. Claims drawn to the subject matter of Group I include: Claims 1 and 2-39 (as they relate to Claim 1 in which X is an optionally substituted aryl or heteroaryl group).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 14, 37, 38, 40, and 41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Claims 1 and 40 recite "spacer group", which is indefinite, since there is no definition of "spacer group" in the Specification.

- The following limitations are unsupported in Claim 2: All of the limitations beginning with: "*Z represents. . .*" through "*. . .or a pharmaceutically-acceptable salt thereof,*" lack antecedent basis, as there is no mention of the definitions of Z or R_2-R_5 in Claim 1, with the exception of "Z represents a spacer group" and "one of the groups R_2, R_3, R_4 and R_5 represents an optionally substituted aryl or *heteroatyl* group." [sic].

- The following limitations are unsupported in Claim 14: "Z represents C_{1-6} alkylene, in which one of the carbon atoms in the chain may be replaced with oxygen."

- Claims 37 and 38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, Claims 37 and 38 reference, "a pharmaceutical formulation including a compound *as defined above*". It is unclear as to which compound described above Applicant refers.

- The following limitation is unsupported in Claim 41: "Z is alkylene" lacks antecedent basis, since there is no mention of the defnition of Z in Claim 40, from which Claim 41 depends and refers to.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32-35 are rejected under 35 U.S.C. 112, first paragraph, because the Specification does not reasonably provide enablement for using compounds of formula (I) for the treatments listed in these claims. Therefore, the Specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

In re Wands, 8 USPQ2d 1400 (1988).

Claim 32 is drawn to a method of treating every disease in which inhibition of the activity of microsomal prostaglandin E synthase-1 (mPGES-1) is desired/required in any host. Claim 33 is drawn to a method of treating inflammation. Claim 34 is drawn to a method of

treating a wide variety of diseases:

> inflammatory bowel disease, irritable bowel syndrome, migraine, headache, low back pain, fibromyalgia, a myofascial disorder, a viral infection, a bacterial infection, a fungal infection, dysmenorrhea, a burn, a surgical or dental procedure, a malignancy, atherosclerosis, gout, arthritis, osteoarthritis, juvenile arthritis, rheumatoid arthritis, rheumatic fever, ankylosing spondylitis, systemic lupus erythematosus, vasculitis, pancreatitis, nephritis, bursitis, conjunctivitis, iritis, scleritis, uveitis, wound healing, dermatitis, eczema, psoriasis, stroke, diabetes, a neurodegenerative disorder, an autoimmune disease, osteoporous, asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, an allergic disorder, rhinitis, an ulcer, coronary heart disease, sarcoidosis or any other disease with an inflammatory component.

Claim 35 is drawn to a method of treating a disease in which the inhibition of the activity of mPGES-1 is desired/required in a person.

Applicant provides no working examples which support the claim to a treatment of any specific diseases. Rather, Applicant provides *in vitro* mPGES-1 inhibition data. Those of skill in the art recognize that *in vitro* assays and/or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking.

The greatly increased complexity of the *in vivo* environment as compared to the very narrowly defined and controlled conditions of an *in vitro* assay does not permit a single extrapolation of *in vitro* assays to human diagnostic efficacy with any reasonable degree of predictability. *In vitro* assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that many differences exist between cultured cells and their counterparts *in vivo*.

These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This result has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences In Vitro).

Further, with respect to the treatment of cancer, which is encompassed by Claims 32, 34, and 35, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions. In view of the teachings above and the lack of guidance, workable examples and or exemplification in the specification, it would require undue experimentation by one of skill in the art to determine with any predictability, that the method would function as claimed.

There is no question Applicant's pyrrolobenzimidazolones *may* play a role in future methods of treating the aforementioned diseases/disorders. What is disputed is the claim that the compounds of formula (I) could be taken by a PHOSITA at the time of filing and used as treatments for the diseases/disorders recited in Claims 32-35, without undue experimentation. At the time of filing or even at present, the most which can be said about the compounds of formula (I) is that certain of the compounds possess the ability to inhibit mPGES-1 *in vitro* Moving from a discovered mechanism of action to a method of treatment requires a fallacious, inductive leap of logic amounting to undue experimentation. There is simply no evidence to be found in the literature suggesting that Applicant's compounds, or their structural cousins, are capable of being used in the manner claimed in Claims 32-35. In essence, there is no absolute predictability in pharmacology, even with compounds whose properties have been determined, despite the extraordinarily high skill possessed by the ordinary artisan.

Another deficiency necessary for a PHOSITA to use Applicant's compounds to treat the recited diseases/disorders is dosage. So far, there is very little, if any, information to be gleaned from the literature on the subject of dosage relating indole-derivatives to those diseases/disorders sought to be treated in the instant Application.

There does not seem to be enough knowledge in the art to connect the compounds' properties to the actual treatment of the diseases/disorders claimed. It does seem that certain indole derivatives capable of inhibiting mPGES-1 may provide useful therapeutic tools in future. Although, at the time of filing, and even at present, a PHOSITA would not be able to use the invention as claimed.

Objections

Claims 1-39 are objected to for containing nonelected subject matter. Claims 3-13, 20-28, and 42 are objected to as they depend from a rejected base claim.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael P. Barker whose telephone number is (571) 272-4341. The examiner can normally be reached on Monday-Friday 8:00 AM- 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Joseph K. McKane, can be reached at (571) 272-0699. The unofficial fax phone for this group are (571) 273-8300.

/Michael P Barker/
Examiner, Art Unit 1626

/Rebecca L Anderson/

Primary Examiner, Art Unit 1626